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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,569	NORRBY, KLAS	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20040824*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *MESH definition*.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Information Disclosure Statement (IDS) submitted 24 August 2004 is acknowledged.

Applicant's preliminary amendment of the claims filed 24 August 2004 has been entered. The restriction requirement mailed on 12 September 2006 was directed to the original claim set. As indicated in the interview summary on 13 October 2006, the restriction requirement is withdrawn.

Claims 1-32 have been cancelled. Claims 33-52 are added. Claims 33-52 are pending and under examination.

Information Disclosure Statement

The information disclosure statement filed 24 August 2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the references in section "Other Documents" refer to STN or Dialog or other search results, which is not a proper form for references categorized as "other documents". It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all

certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Specification

The Abstract is objected for using legal phraseology "said" and "disclosed". Appropriate correction is required.

Claim Objections

Claims 33, 40 are objected to because of the following informalities:

Claims 33 and 40 need a ";" after "administering...to the patient".

Claim 40 recites "selecting a peptide from the group consisting of peptides derivable from human lactoferrin". It is an improper Markush group.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-52 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for treatment or prevention of a vascular disease or states of tissue hypoperfusion with hypoxic or ischemic consequences in a patient, comprising administering a therapeutically effective amount of a substance selected from the group consisting of human apo-lactoferrin, human lactoferincin, peptides derivable from human lactoferrin, natural metabolites of human lactoferrin, and functionally equivalent analogues of human apo-lactoferrin, wherein the peptide comprises a peptide constituted of all or some of the amino acid residues of 12-40 of human lactoferrin or a modified version thereof (claim 41), or the peptide is formed from the sequences constituted of amino acid residues 16-40 and 18-40 of human lactoferrin or a modified version thereof (claim 42), or the peptide essentially corresponds to residues 18-31 of human lactoferrin with C20A, Q22K and N26D amino acid changes (claim 43), or the peptide is formed of amino acids in positions 12-31 in the sequence constituting human lactoferrin or a modified version thereof, or a fragment thereof consisting of at least 7 amino acids (claim 44), or the peptide consists of 11-17 amino acids corresponding to the sequences that begin with one of the amino acids in positions 15-21 and end with the amino acid in position 31 in the sequence constituting human lactoferrin or a modified version thereof (claim 45), or the peptide consists of 12 amino acids based on the sequence consisting of the amino acid in positions 20-31 of human lactoferrin.

The claims are broad in that the recitations of "peptides derivable from human lactoferrin", "natural metabolites of human lactoferrin", and "functionally equivalent analogues of human apo-lactoferrin" encompass a large genus of molecules, known or

unknown, with a diverse range of structures and functions. What applicant has described in the specification are human apo-lactoferrin, and its natural metabolite, lactoferricin, generated by pepsin-cleavage from human lactoferrin. Applicant describes that the peptides include those disclosed in the sequence listing of WO 00/01730 (pp. 4, line 25 to pp. 5, line 6). Applicant, however, has not described the genus of peptides, natural metabolites, and functionally equivalent analogues of human apo-lactoferrin. There is no teaching regarding the relationship of structure to function, such as what structural feature these molecules have. Further, there is no requirement that these molecules have any particular function. Thus, the claims encompass a genus of molecules, which vary substantially in composition, and could have very different structural and functional characteristics from the products that Applicant has disclosed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making of the claimed product, or any combination thereof. In this case, there is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of peptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only human apo-lactoferrin, its natural metabolite lactoferricin, and the peptides disclosed in the sequence listing of WO 00/01730, but not the full scope of the claimed substance is adequately described in the disclosure.

Claims 33-52 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method for treatment of states of tissue hypoperfusion due to hypoxia or ischemia in a patient afflicted with the disease or*

condition, comprising administering to the patient a therapeutically effective amount of a substance selected from the group consisting of human apo-lactoferrin and human lactoferricin, whereby the method is used as an alternative to bypass or therapeutic angiogenesis treatments used in treating such a disease or physiological condition, does not reasonably provide enablement for: 1) administering other substances; 2) treating any vascular disease, or in any patient; and 3) preventing any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broad in that they encompass and require the use of a large genus of substances for treating any vascular disease or in any patient. The

specification discloses that human apo-lactoferrin stimulates $VEGF_{165}$ induced angiogenesis, and has a pro-angiogenic effect, which can be used for therapeutic angiogenesis. The specification, however, does not provide sufficient support for the genus of substances, i.e., peptides derivable from human lactoferrin, natural metabolites of human lactoferrin, and functionally equivalent analogues of human apo-lactoferrin, that can be used in therapeutic angiogenesis. The specification describes that the peptides include those disclosed in the sequence listing of WO 00/01730. However, the peptides disclosed in the WO 00/01730 have different properties, and exhibit anti-inflammatory, anti-infectious and anti-tumoral activities. WO 00/01730 describes that "the peptides according to the invention are fungicidal and bactericidal, and can be used for treatment of infections, inflammations and tumors" (pp. 4, lines 22-28). It is well known that molecules that exhibit inhibition of angiogenesis can be used as an anti-tumor agent. The specification has not shown any of these peptides that act in the same mode as human lactoferrin. Further, the peptides recited in claims 41-46 can have the same amino acid sequences as fragments generated from bovine apo-lactoferrin, which, as indicated in the specification and demonstrated in the reference of Nobby et al. (Int. J. Cnacer, 2001, 91:236-240), on the contrary to human apo-lactoferrin, significantly inhibits $VEGF_{165}$ induced angiogenesis. Since the specification has not presented sufficient support, nor provided working examples, for these peptides, metabolites and analogues recited in the claims, one of skill in the art would not know how to use such substances. It would requires a large quantity of experimentation to determine what activities these molecules have, and whether they

can be useful in treating the vascular diseases, and such experimentation would be undue.

In addition, the claims read on treating any vascular disease and in any patient (without specifying a disease). The specification teaches that human apo-lactoferrin enhances $VEGF_{165}$ induced angiogenesis, and can be used to treat a vascular disease having a consequence of tissue damage. The specification teaches that such tissue damage is typically caused by occlusive or non-occlusive vascular disease leading to tissue hypoxia or ischemia. Such tissue hypoxia or ischemia may be exemplified by impending or manifested infarction such as myocardial infarction, stroke, gangrene, or angina pectoris. Other clinical conditions that would benefit from enhanced $VEGF_{165}$ induced angiogenesis are various types of wound healing situations such as in peptic ulcers and leg ulcers. Certain types of male hair loss, such as androgenic alopecia, might also be a condition where enhanced angiogenesis might be beneficial. The specification teaches that a common denominator for all these ischemic and/or hypoxic conditions is the resulting local expression or biological effect of VEGF. The specification has not provided support for treating other vascular diseases, nor in a patient with any disease. Vascular diseases include a wide variety of different diseases (see MESH definition), with many causes, strike different tissues and have different outcomes. The specification does not teach treatment for such broadly claimed diseases. Further, the claims recite prophylaxis of a vascular disease. However, there is no guidance as to how to prevent a vascular disease in a subject. Since the specification fails to provide guidance for treating any vascular disease or preventing a

vascular disease in any subject, which would be encompassed by the claims, the skilled artisan could not predictably identify all individuals who might need to be treated to prevent such a disease. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification.

Due to the large quantity of experimentation necessary to determine the nearly infinite number of substances for their uses to prevent or treat a vascular disease in any subject, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide the therapeutic uses, and in which patient population, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of structure on function, and the breadth of the claims which fails to recite any structural limitations and reads on any vascular disease in any subject, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33, 34, 40, 42, 46, 47 and 49-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33 and 40 are indefinite for the recitation of "states of tissue hypoperfusion with hypoxic or ischemic consequences". It is unclear whether the claim is intended to mean "tissue hypoperfusion as a consequence of hypoxia or ischemia" or "tissue hypoperfusion leading to hypoxia or ischemia".

Regarding claims 34 and 47, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 34 and 47 are also indefinite for the recitation "peripheral artery occlusive disease with or without impending gangrene". Impending gangrene means that gangrene is about to occur (but has not yet occurred). Without impending gangrene means it will never occur. The claims are unclear for the recited disease status.

Claims 40 and 49-52 recite the limitation of "the selected substance" or "said substance". There is insufficient antecedent basis for this limitation in the claims.

Claim 42 is indefinite for the recitation of "the peptide comprises a peptide formed of the sequences constituted of amino acids 16-40 and amino acids 18-40 from the N-terminal end of human lactoferrin". It is unclear if the claim is intended to mean that the peptide is formed from the sequence set forth in the amino acid residues 16-40 or from the sequence set forth in the amino acid residues 18-40 of human lactoferrin, or the peptide is formed from the both sequences, i.e., the peptide comprises both sequences.

Claim 46 is indefinite for the recitation "based on the sequence". It is unclear if the claim requires the peptide having identical amino acid sequence as residues 20-31 of human lactoferrin, or allows amino acid changes in the sequence.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33-38 and 40-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Mamoru et al. (JP 07-278011, Date of publication: 24 October 1995).

The instant claims are drawn to a method of treatment of a vascular disease or states of tissue hypoperfusion due to hypoxia or ischemia in a patient in need of the treatment, comprising administering a therapeutically effective amount of a substance selected from the group consisting of human apo-lactoferrin, human lactoferricin, and peptides, metabolites and analogues thereof, whereby the method is used as an alternative to by-pass surgery or any therapeutic angiogenesis option (claims 33, 35, 40, 48); wherein the peptide comprises all or some of the amino acid residues of 12-40 of human lactoferrin (claim 41), or the peptide is formed from the sequences of amino acid residues 16-40 or 18-40 of human lactoferrin (claim 42), or the peptide essentially corresponds to amino acid residues 18-31 of human lactoferrin with C20A, Q22K and N26D amino acid changes (claim 43), or the peptide is formed of amino acid residues 12-31 or a fragment thereof consisting at least 7 amino acids (claim 44), or the peptide consists of 11-17 amino acids corresponding to the sequences that begin with one of the amino acid residues 15-21 and end with the amino acid residue 31 (claim 45), or the

peptide consists of 12 amino acids based on the sequence consisting of the amino acid residues 20-31 of human lactoferrin (claim 46); wherein the method is used for treating, for example, stroke, angina pectoris, myocardial infarction, and peripheral artery occlusive disease (claims 34, 47); wherein the substance is administered orally, parenterally, or locally (claims 36-38, 49-51).

JP 07-278011 teaches a method of treating angina pectoris comprising administering to a patient afflicted with the disease a therapeutically effective amount of an agent comprising a peptide of human lactoferrin (see Abstract and [0014]). JP 07-278011 teaches various peptides (see [0035]-[0066]), which meet the limitations for the peptides recited in claims 41-46, since these claims encompass peptides with changes or modifications of the sequences of human lactoferrin. JP 07-278011 teaches that therapeutic agent is parenterally (locally) or orally administered (see Abstract and [0017]). Therefore, JP 07-278011 anticipates the instant claims.

Claims 33-52 are further rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al. (U. S. Patent No: 5,712,247, issued on 27 January 1998).
The '247 patent teaches a method of treating a vascular disease, e.g., a heparin-induced prolongation of blood coagulation and other coagulapathies in cardiopulmonary bypass, cardio catheterization and hemodialysis patients, comprising administration of lactoferrin or fragments thereof (see Abstract). Patients that need cardiopulmonary bypass or cardio catheterization usually have angina, having a limitation of blood supply through the narrowed arteries and the resulting myocardial ischaemia, and

revascularisation (restoration of adequate blood supply to the heart muscle) by using coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) may also be needed (see Drug Ther. Bull., 2007, 45(2):12-6). The '247 patent teaches using recombinant human lactoferrin (column 4, lines 45-49) and N-terminal lactoferrin peptides (column 15, line 57 through column 16, lines 31), which meet the limitations for the peptides recited in claims 41-46, since these claims encompass peptides with changes or modifications of the sequences of human lactoferrin. The '247 patent teaches routes of administration, e.g., systemic or local administration, oral, intranasal (inhalation), or parenteral administration (column 5, lines 18-26). Therefore, the '247 patent anticipates the instant claims.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
May 14, 2007

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER